Prenatal Maternal Smoking and Tourette Syndrome: A Nationwide Register Study

Leivonen, Susanna

2016

Leivonen , S , Chudal , R , Joelsson , P , Ekblad , M , Suominen , A , Brown , A S , Gissler , M , Voutilainen , A & Sourander , A 2016 , ' Prenatal Maternal Smoking and Tourette Syndrome: A Nationwide Register Study ' , Child Psychiatry and Human Development , vol. 47 , no. 1 , pp. 75-82 . https://doi.org/10.1007/s10578-015-0545-z

http://hdl.handle.net/10138/223856
https://doi.org/10.1007/s10578-015-0545-z

publishedVersion

Child Psychiatry Hum Dev (2016) 47:75–82
DOI 10.1007/s10578-015-0545-z

ORIGINAL ARTICLE

Prenatal Maternal Smoking and Tourette Syndrome: A Nationwide Register Study

Susanna Leivonen[1,2] · Roshan Chudal[1] · Petteri Joelsson[1] · Mikael Ekblad[3] · Auli Suominen[1] · Alan S. Brown[4,5] · Mika Gissler[1,6,7] · Arja Voutilainen[2] · Andre Sourander[1,8,9]

Published online: 22 March 2015

Abstract This is the first nationwide register-based study to examine the relationship between prenatal maternal smoking and Tourette syndrome. A total of 767 children diagnosed with Tourette syndrome were identified from the Finnish Hospital Discharge Register. Each case was matched to four controls. Information on maternal smoking during pregnancy was obtained from the Finnish Medical Birth Register. Conditional logistic regression models were used for statistical analyses. Prenatal maternal smoking was associated with Tourette syndrome when comorbid with ADHD (OR 4.0, 95 % CI 1.2–13.5, $p = 0.027$ for exposure during first trimester, OR 1.7, 95 % CI, 1.05–2.7, $p = 0.031$ for exposure for the whole pregnancy). There was no association between maternal smoking during pregnancy and Tourette syndrome without comorbid ADHD (OR 0.5, 95 % CI 0.2–1.3, $p = 0.166$, OR 0.9, 95 % CI 0.7–1.3, $p = 0.567$). Further research is needed to elucidate the mechanisms behind the association between prenatal maternal smoking and Tourette syndrome with comorbid ADHD.

Keywords Tourette syndrome · Prenatal maternal smoking · ADHD · Register study · Epidemiology · Risk factor

Abbreviations

TS	Tourette syndrome
ADHD	Attention deficit hyperactivity disorder
FHDR	Finnish Hospital Discharge Register
FMBR	Finnish Medical Birth Register
ICD	International Classification of Diseases
DSM-5	Diagnostic and statistical manual of mental disorders, 5th edition

Introduction

Tourette syndrome (TS) is a childhood onset neurodevelopmental disorder characterized by a combination of vocal and multiple motor tics [1]. The etiology of TS remains unclear. In addition to a likely complex genetic basis, a number of environmental factors, including pre-, peri- and postnatal adversities, may contribute to the pathogenesis of TS [2–4] although the mechanisms are still unknown. TS is often accompanied by other neurodevelopmental disorders, including ADHD, and other psychopathology [5, 6]. The prevalence of TS in children and adolescents is 0.7 % [7].

✉ Susanna Leivonen
susanna.leivonen@utu.fi

1 Department of Child Psychiatry, University of Turku, Turku, Finland

2 Child Neurology, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

3 Department of Pediatrics, Turku University Hospital and University of Turku, Turku, Finland

4 Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York State Psychiatric Institute, New York, NY, USA

5 Department of Epidemiology, Columbia University, Mailman School of Public Health, New York, NY, USA

6 National Institute of Health and Welfare (THL), Helsinki, Finland

7 Nordic School of Public Health, Gothenburg, Sweden

8 Department of Child Psychiatry, Turku University Hospital, Turku, Finland

9 RKBU, UiT Arctic University in Norway, Tromsø, Norway

No prevalence studies of TS have been conducted in Finland, however, the prevalence of TS seems to be similar in many countries [7].The register-based incidences and prevalence of diagnosed TS and other tic disorders have been increasing both in Finland and other Nordic countries [8, 9]. Prevalence of attention deficit/hyperactivity disorder in an adolescent Finnish population was 8.5 % according to DSM-4 classification [10]. In a register-based data, 28 % of children diagnosed with TS specialized health care in Finland were also diagnosed with hyperkinetic disorder [8]. There are some differences between ADHD in DSM-5 and hyperkinetic disorder in ICD-10 [1, 11]. DSM-5 recognizes inattentive presentation and hyperactive-impulsive presentation when ICD-10 includes disturbance of activity and attention (F90.0), hyperkinetic conduct disorder (F90.1), other hyperkinetic disorders (F90.8) and hyperkinetic disorder unspecified (F90.9). However, the similarity between ADHD in DSM-5 and hyperkinetic disorders in ICD-10 is obvious as they recognize the same behavioral characteristics [1, 11]. We refer both hyperkinetic disorders in ICD-10 and ADHD in DSM-5 as ADHD in the following text.

Smoking is still a considerable problem among pregnant women, in Finland 15 % of women smoke during pregnancy [12]. Smoking during pregnancy has been related to neurodevelopmental disorders, including ADHD [13–20]. Prenatal maternal smoking has been associated with increased tic severity [21] and comorbid ADHD or OCD [22, 23], but the studies are few with inconsistent results [21–25]. The inconsistencies could be explained by relatively small sample sizes, retrospective data collection, limited consideration for confounding factors, inconsistent study populations and outcome definitions [3, 4, 21–25]. There is only one prospective population-based study of the association between prenatal maternal smoking and TS. The study, derived from the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort, did not find an association between prenatal maternal smoking and onset of TS [26].However, the sample size was limited to 50 children with TS, the children with TS with comorbid ADHD were not studied separately and the diagnoses were based on questionnaires completed by mothers [6, 26].

The etiology of TS remains unclear, prenatal maternal smoking can be influenced by counselling, and the incidence of TS could be increasing. Thus, it is important to clarify the association between prenatal maternal smoking and TS in a large cohort. To our knowledge, the present study is the first nationwide register-based study examining the association between prenatal maternal smoking and TS. The aim of the study was to examine if prenatal maternal smoking is associated with TS. Furthermore, since TS and ADHD are highly comorbid, and there is an established association between prenatal maternal smoking and ADHD, the additional aim was to examine whether the association is different among children with TS with and without comorbid ADHD.

Methods

This study is part of the Finnish Prenatal Study of Tourette Syndrome and Other Tic Disorders (FIPS-TIC) examining pre- and perinatal risk factors for TS. FIPS-TIC is a nationwide register study based on a nested case–control design. The sampling frame included all 1199 112 children born in Finland between 1st January 1991 and 31st December 2010 [27]. The design was based on linking the data from three national registers: Finnish Hospital Discharge Register (FHDR), Finnish Medical Birth Register (FMBR) and Finnish Central Population Register. The cases and controls were identified from the FHDR and the Finnish Central Population Register, respectively. Linking was achieved by using personal identity codes (PIC), which are assigned to all Finnish citizens and residents by the Central Population Register since 1971. The study was authorized by the Ministry of Social Affairs and Health (STM/1528/2007) and the National Institute of Health and Welfare (THL) with approval from the ethics committee of the hospital district of Southwest Finland.

National Register Information

The FHDR includes a primary diagnosis and possible subsidiary diagnoses for each patient at discharge. This information is based on clinical diagnoses. The diagnostic assessment of neurodevelopmental disorders in specialized health care in Finland is led by a child psychiatrist or pediatric neurologist. The diagnoses are given based on ICD-10 criteria. TS diagnosis is based on clinical assessment and interview accompanied with questionnaires. Psychological assessment and other differential diagnostic examinations are conducted when necessary. There is a national guideline for diagnosing and treating ADHD [28]. ADHD diagnosis is based on a comprehensive assessment including clinical assessment and interviews of the parents using structured questionnaires and collecting data from childs environment e.g. school. Cognitive capacity is examined by psychologists. When necessary, due to comorbidities and/or differential diagnostic issues, the child is examined also by other professionals e.g. speech- or occupational therapists. The FHDR was established in the 1960s and it covers all Finnish psychiatric hospitals, inpatient wards of local health care centers, military wards, prison hospitals and private hospitals since 1969 and outpatient clinics at the public hospitals since 1998. A systematic review of the quality of the FHDR showed that the accuracy of diagnosis in the register varied from

satisfactory to very good as the positive predictive value (proportion of register-detected cases that were confirmed to be true positives according to the external data) varied between 75 and 99 % [29]. Furthermore, the validity of TS diagnoses in the FHDR has been studied by chart reviews and telephone interviews based on the Yale Global Tic Severity Scale and the validity of the diagnosis was shown to be 95 % [8].

The FMBR includes standardized data on pregnancies, prenatal period and neonatal period up to 7 days of age from 1987 onwards on all births in Finland. Data on maternal smoking during pregnancy were derived from the FMBR based on information collected at maternity clinics during obstetric visits. According to THL, 99.7 % of pregnant women in Finland visit a maternity clinic. Data on smoking during pregnancy was divided into three categories: no smoking, smoking during the first trimester only, and smoking throughout the pregnancy.

The Finnish Central Population Register contains personal data about Finnish citizens and other citizens residing permanently in Finland. The data contains basic information including name, personal identity code (PIC), address, citizenship and native language, family relations, emigration and immigration dates and countries and dates of birth and death. The PIC includes date of birth, sex and a unique control number for each person. Parents of the cases and controls were identified from the Finnish Central Population Register.

The Identification of the Cases and Controls

Children diagnosed with TS (ICD-10 code F95.2 or ICD-9 code 3072D), excluding only children with severe or profound mental retardation (ICD-10 codes F72, F73 and ICD-9 codes 3181 and 3182), between 1st January 1991 and 31st December 2010 were identified from the FHDR (n = 767). The children with severe and profound mental retardation were excluded due to more difficult diagnostic evaluation of TS in these children. The most recent diagnosis was used. Children born twins (n = 24) or triplets (n = 1) were excluded to ascertain that no other factors related to these risk pregnancies influenced the results since it was unlikely to find controls fulfilling the matching criteria and requirement of twin or triplet pregnancy. Data on maternal smoking was found on 723 out of 742 remaining cases. There were 114 (15.8 %) females and 609 (84.2 %) males. The mean age of TS diagnosis was 9.5 years (standard deviation 2.8). Data on maternal socioeconomic status was found on 663 (91.7 %) cases and 103 (15.5 %) were upper white collar workers, 283 (42.7 %) were lower white collar workers, 160 (24.1 %) blue collar workers and 117 (17.7 %) others. The children with TS were stratified into two groups: TS without and with comorbid ADHD (ICD-10 codes: F90.0, F90.1, F90.8, F90.9 and ICD-9 codes: 314X).

The controls, defined as children without any tic disorder or severe or profound mental retardation, were identified from the Finnish Central Population Register. Children with other health conditions/diagnoses were not excluded. Each case was matched to four controls, on date of birth, sex and place of birth. Furthermore, those who emigrated from Finland (n = 9), who died before the case was diagnosed (n = 12), as well as the controls born from twin or triple pregnancies (n = 87), or whose case was born from twin or triplet pregnancy (n = 98) or for whom data on maternal smoking was absent (n = 68), were excluded. The number of remaining controls with data on maternal smoking was 2698.

Potential Confounding Factors

Trend of association ($p < 0.10$) was tested between nine potential confounding factors associated with both prenatal maternal smoking and TS or other neurodevelopmental disorders including ADHD and autism [3, 4, 14, 30–42]. Maternal and paternal age at time of birth were divided into four categories (<20, 20–29, 30–39, ≥40 years). Maternal and paternal psychiatric histories were classified dichotomously (yes/no). A parent was classified as having a psychiatric history if they had any mental disorder of F10-F99 disorder based on ICD-10 excluding mental retardation F70- F79. Corresponding diagnoses based on ICD-9 (any mental disorder 291–316, excluding organic psychiatric conditions 293–294 and 310) and ICD-8 (any mental disorder 291–308, excluding organic psychiatric conditions 292-294 (except intoxication 294.30) and conditions due to sexuality 302) were utilized during the period those diagnostic systems were in use. Maternal socioeconomic status was based on occupation during pregnancy and classified in four categories: upper white collar, lower white collar, blue collar and others. Parity was classified dichotomously 0 or ≥1. Birth weight and gestational age were classified as dichotomous variables: <2500 or ≥2500 grams and <37 weeks or ≥37 weeks. Apgar at 1 min was classified as 0–6 or 7–10. Data on parental age were derived from the Central Population Register, data on parental psychopathology were derived from the FHDR, and the rest of data were from the FMBR.

Statistical Analyses

Bivariate analyses were conducted to test the trend of association between potential confounding factors, described in the previous section, and maternal smoking during pregnancy among the controls as well as between potential confounding factors and TS. Conditional logistic

regression analysis was used to examine the association between prenatal maternal smoking and TS. Smoking was categorized as "no smoking", "smoking during the first trimester only" and "smoking throughout pregnancy". First, the unadjusted odds ratios (ORs) and 95 % confidence intervals (CIs) were calculated for the whole TS group with the limit of statistical significance of $p < 0.05$. Second, the ORs were adjusted for the selected confounding factors. Finally, the unadjusted and adjusted ORs were calculated separately in data where cases were with and without co-morbid ADHD. Statistical analyses were performed with SAS statistical software (Version 9.4; SAS Institute Inc., Cary, NC).

Results

Maternal age, psychiatric history and socioeconomic status, paternal age and psychiatric history as well as birthweight and gestational age showed a trend of association ($p < 0.10$) for both maternal smoking during pregnancy among the controls and TS. These covariates were included in the further analyses. Apgar score at 1 min did not show a trend of association with maternal smoking during pregnancy or TS, and therefore it was not included in the further analyses (Table 1).

Among the TS group, 137 (18.9 %) cases and 397 (14.7 %) controls were exposed to prenatal maternal smoking during pregnancy (Table 2). The majority of the exposed cases (n = 121, 16.7 %) and controls (n = 356, 13.2 %) were exposed throughout the pregnancy. After adjusting for the confounding factors neither prenatal maternal smoking during the first trimester or throughout the pregnancy was associated with offspring TS (OR 1.1, 95 % CI 0.8–1.4 and OR 1.1, 95 % CI 0.5–2.2, respectively).

The sample was stratified into two groups: TS cases without (n = 520, 72 %) comorbid ADHD and TS cases with comorbid ADHD (n = 203, 28 %). Maternal smoking during the first trimester and throughout pregnancy was associated with TS with comorbid ADHD (OR 4.0, 95 % CI 1.2–13.5, OR 1.7, 95 % CI 1.05–2.7, respectively). However, no significant association was found between smoking during first trimester or throughout pregnancy when TS was not comorbid with ADHD (OR 0.5, 95 % CI 0.2–1.3, OR 0.9, 95 % CI 0.7–1.3, respectively).

Discussion

Our results provide evidence that maternal smoking during pregnancy has a different relationship in children with TS with, and without, comorbid ADHD. Maternal smoking during pregnancy was associated with TS with comorbid ADHD, but not with TS without ADHD. The odds ratios for TS with comorbid ADHD were higher when smoking occurred only during the first trimester compared to throughout pregnancy. However, that is likely to be explained by the small number of the children in this group leading to larger dispersion in relation to number of the cases and less accurate statistical estimation. This is supported by the more dispersed confidence interval compared with the larger group exposed throughout the pregnancy. One intriguing question is: What are the underlying mechanisms for the difference between TS with and without ADHD in relation to maternal smoking during pregnancy? The relationship between prenatal maternal smoking during pregnancy and ADHD has been established [15–20]. However, the nature of the relationship is not fully elucidated. Nicotine has been shown to be neurotoxic in both animal and human studies [43, 44]. Animal studies have demonstrated an association between prenatal nicotine exposure and up-regulation of nicotinic acetylcholine receptors and dysregulation in several neurotransmitter systems in different regions of the brain [45]. Human studies have shown structural and functional changes in the brain associated with prenatal maternal smoking [45, 46]. As nicotine crosses the placenta during pregnancy [47] a direct intrauterine effect seems biologically plausible. However, several studies have suggested that the association between prenatal maternal smoking and ADHD is, at least partly, due to environmental or genetic confounding factors than a direct intrauterine effect [15, 20, 48].

TS and ADHD co-occur frequently [5, 6, 8], but the relationship between these two disorders remains unclear and debated. These disorders may share genetic factors [49] and also involve partly similar morphological changes in the brain [50]. Recent data reduction studies have identified different phenotypes of TS based on simplicity or complexity of tics, co-occurrence of ADHD and obsessive–compulsive disorder and psychopathology [51–53]. Males have been overrepresented in a phenotype having both TS/tic disorder and ADHD [52]. Furthermore, it has been suggested that disruptive behavioral, mood and anxiety disorders may be accounted for by comorbid ADHD in children with TS [54]. TS/ADHD might reflect a separate entity rather than two co-morbid disorders [55].

Interactions between psychosocial factors and genotype have been suggested to be involved in the etiology of ADHD [56]. Gene-environmental interactions involving prenatal maternal smoking and ADHD [57] have also been suggested, though the studies are not unequivocal [58]. Gene-environmental interactions in the etiology of TS have not been a major focus of research yet. However, Bos-Veneman et al. [24] suggested that the relationship between in utero smoking exposure and ADHD symptom severity in children with TS or chronic tic disorder was more

Table 1 Potential confounding factors in relation to maternal smoking during pregnancy in controls and TS, respectively

	Relationship between covariates and smoking during pregnancy			Relationship between covariates and TS
	No smoking	Smoking		
	n (%)	n (%)	p^a	p^b
Maternal psychiatric history			<.001	<.001
No	2059 (89.5)	316 (79.6)		
Yes	242 (10.5)	81 (20.4)		
Paternal psychiatric history			<.001	<.001
No	2060 (89.9)	283 (73.1)		
Yes	232 (10.1)	104 (26.9)		
Maternal age			<.001	.004
<20	46 (2.0)	26 (6.6)		
20–29	1146 (49.8)	240 (60.5)		
30–39	1046 (45.5)	123 (31.0)		
≥40	63 (2.7)	8 (2.0)		
Paternal age			.001	.004
<20	12 (0.5)	3 (0.8)		
20–29	836 (36.5)	180 (46.5)		
30–39	1230 (53.7)	169 (43.7)		
≥40	214 (9.3)	35 (9.0)		
Birth weight			.008	.076
<2500	60 (2.6)	20 (5.0)		
≥2500	2241 (97.4)	377 (95.0)		
Gestational age			.018	.044
<37 weeks	95 (4.1)	27 (6.8)		
≥37 weeks	2202 (95.9)	370 (93.2)		
Maternal socioeconomic status			<.001	.001
Upper white collar worker	346 (16.1)	19 (5.2)		
Lower white collar	1104 (51.4)	151 (41.3)		
Blue collar	339 (15.8)	121 (33.1)		
Other	357 (16.6)	75 (20.5)		
Parity			.517	<.001
0	940 (40.9)	169 (42.7)		
≥1	1356 (59.1)	227 (57.3)		
Apgar score at 1 min			.682	.138
0–6	83 (3.6)	16 (4.0)		
7–10	2215 (96.4)	381 (96.0)		

[a] p values calculated using Pearson's χ^2-test

[b] Conditional logistic regression was used to examine the association

pronounced in children with a positive family history of mental disorders. This could indicate that gene-environmental interactions affect the TS/ADHD phenotype.

The strengths of the register-based study design include large sample size, elimination of participation and re-call biases, and availability of data on several potential confounding factors. Furthermore, diagnoses were made by specialized healthcare services and the validity of the TS diagnoses in the FHDR was demonstrated to be high [8]. Virtually, all children in Finland visit child health clinics and school health services several times during childhood and adolescence and it is likely that the children with moderate or severe TS are identified, referred to specialist clinics, and therefore, found in the FHDR. However, some of the children with mild TS may not be referred to specialized services [8] and therefore not recorded in the FHDR. Another limitation is that design of the study was based on identification of the children with TS, and therefore children with

Table 2 Associations between prenatal maternal smoking and TS, TS with comorbid ADHD and TS without comorbid ADHD

Tourette syndrome						
Smoking	Distribution of the participants by exposure		Unadjusted		Adjusted	
	Cases, n (%)	Controls, n (%)	OR (95 % CI)	*p*	OR[b](95 % CI)	*p*
Tourette syndrome, all cases						
No	586 (81.1)	2301 (85.3)	1.0[a]		1.0[a]	
Only 1st trimester	16 (2.2)	41 (1.5)	1.5 (0.8–2.8)	.157	1.1 (0.8–1.4)	.835
Throughout pregnancy	121 (16.7)	356 (13.2)	1.3 (1.1–1.7)	.010	1.1 (0.5–2.2)	.574
Tourette syndrome with comorbid ADHD						
No	148 (72.9)	855 (86.9)	1.0[a]		1.0[a]	
Only 1st trimester	9 (4.4)	8 (1.1)	5.1 (1.9–13.4)	.001	4.0 (1.2–13.5)	.027
Throughout pregnancy	46 (22.7)	91 (12.1)	2.2 (1.5–3.3)	<.001	1.7 (1.–2.7)	.031
Tourette syndrome without comorbid ADHD						
No	438 (84.2)	1646 (84.7)	1.0[a]		1.0[a]	
Only 1st trimester	7 (1.4)	33 (1.7)	0.8 (0.3–1.8)	.550	0.5 (0.2–1.3)	.166
Throughout pregnancy	75 (14.4)	265 (13.6)	1.1 (0.8–1.4)	.656	0.9 (0.7–1.3)	.567

[a] Reference

[b] adjusted for maternal and paternal psychiatric history, maternal and paternal age, birth weight, gestational age and maternal socioeconomic status

ADHD and without TS were not included into our study. Thus, we are not able to assess whether the association between prenatal maternal smoking and TS and ADHD is additive compared to ADHD only. Furthermore, since there are differences between diagnostic criteria for ADHD and hyperkinetic disorders the comparisons across different studies using different diagnostic criteria should be interpreted with caution. However, since the diagnoses are mainly overlapping and the diagnostic criteria for hyperkinetic disorder in ICD-10 are more strict than criteria for ADHD in DSM-5, the children in our study are likely to fulfill the DSM-5 criteria. In the light of the other studies, the additive model seems unlikely because in pooled analyses the estimated odds ratio for ADHD in association to prenatal maternal smoking was 2.4 [34]. Maternal smoking during pregnancy was based on self-reports which may lead to underestimation of smoking [59]. Furthermore, the register does not record the level of smoking and thus, it was not possible to assess whether the number of smoked cigarettes was of importance. Finally, information about other exposures to smoking (e.g. passive, paternal and postnatal) or other substance abuse is lacking in the register and it is impossible to assess the impact of these on the outcomes.

Summary

Prenatal maternal smoking is associated with TS when comorbid with ADHD. Since the clinical consequences of comorbid ADHD in children with TS are significant, it is of importance to inform future parents with familial loading for TS of the increased risk for comorbid TS and ADHD associated with maternal smoking during pregnancy among all the other risks related to maternal smoking. Maternal smoking should also be considered as a risk factor when assessing the comorbidities in a child with TS. The association between prenatal maternal smoking and TS with comorbid ADHD is most likely explained by the established relationship between prenatal maternal smoking and ADHD. In future studies a design including cases also with ADHD without TS is needed to substantiate this. However, in the light of recent studies indicating shared inherited factors for the different neurodevelopmental disorders further research is needed to address the intriguing question of whether the different gene-environmental interactions may explain co-occurrence and the different phenotypes of neurodevelopmental disorders.

Acknowledgments The study was supported by grants from Tourette Syndrome Association (USA), Finnish Brain Foundation (Finland) and the Sigrid Juselius Foundation (Finland). We thank our collegues at the Research Center for Child Psychiatry at University of Turku, especially Juha-Pekka Virtanen who was responsible for data management. We thank the Tourette Syndrome Association, Finnish Brain Foundation and the Sigrid Juselius Foundation for financial support.

References

1. World Health Organization (1992) International classification of diseases, 10th revision (ICD-10). Switzerland, Geneva

2. Deng H, Gao K, Jankovic J (2012) The genetics of Tourette syndrome. Nat Rev Neurol 8:203–213
3. Chao T-K, Jing H, Pringshem T (2014) Prenatal risk factors for Tourette syndrome: a systematic review. BMC Pregnancy Childbirth 14:53
4. Hoekstra PJ, Dietrich A, Edwards MJ, Elamin I, Martino D (2013) Environmental factors in Tourette syndrome. Neurosci Biobehav Rev 37:1040–1049
5. Freeman R, Fast D, Burd L, Kerbeshian J, Robertson M, Sandor P (2000) An international perspective on Tourette syndrome: selected findings from 3500 individuals in 22 countries. Dev Med Child Neurol 42:436–447
6. Scharf J, Miller L, Mathews C, Ben-Shlomo Y (2011) Prevalence of Tourette Syndrome and Chronic Tics in the Population Based Avon Longitudinal Study of Parents and Child Cohort. J Am Acad Child Adolesc Psychiatry 5:192–201
7. Knight T, Steeves T, Day L, Lowerison M, Jette N, Pringshem T (2012) Prevalence of tic disorders: a systematic review and meta-analysis. Pediatr Neurol 47:77–90
8. Leivonen S, Voutilainen A, Hinkka-Yli-Salomäki S, Timonen-Soivio L, Chudal R, Gissler M et al (2014) A register study of the characteristics, incidence and validity of diagnosed Tourette syndrome and other tic disorders. Acta Paediatr 103:984–990
9. Atladottir H, Gyllenberg D, Lanrigde A, Sandin S, Hansen S, Leonard H et al (2015) The increasing prevalence of reported diagnoses of childhood psychiatric disorders: a descriptive multinational comparison. Eur Child Adolesc Psychiatry 24:173–183
10. Smalley SL, McGough JJ, Moilanen IK, Loo S, Taanila A, Ebeling H et al (2007) Prevalence and psychiatric comorbidity of attention-deficit/hyperactivity disorder in an adolescent Finnish population. J Am Acad Child Adolesc Psychiatry 46:1575–1583
11. American Psychiatric Association (2013) Diagnostic and Statistical Manual of Mental Disorders, 5th edition. Arlington, VA., American Psychiatric Association
12. Ekblad M, Gissler M, Korkeila J, Lehtonen L (2014) Trends and risk groups for smoking during pregnancy in Finland and other Nordic countries. Eur J Public Health 24:544–551
13. Tran PL, Lehti V, Lampi KM, Helenius H, Suominen A, Gissler M, Brown AS, Sourander A (2013) Smoking during pregnancy and risk of autism spectrum disorder in a finnish national birth cohort. Paediatr Perinat Epidemiol 27:266–274
14. Hultman CM, Sparen P, Cnattingius S (2002) Perinatal risk factors for infantile autism. Epidemiology 13:417–423
15. Lindblad F, Hjern A (2010) ADHD after fetal exposure to maternal smoking. Nicotine Tob Res 4:408–415
16. Langley K, Rice F, van den Bree MB, Thapar A (2005) Maternal smoking during pregnancy as an environmental risk factor for attention deficit hyperactivity disorder behaviour: a review. Minerva Pediatr 57:359–371
17. Mick E, Biederman J, Faraone SV, Sayer J, Kleinman S (2002) Case–control study of attention-deficit hyperactivity disorder and maternal smoking, alcohol use, and drug use during pregnancy. J Am Acad Child Adolesc Psychiatry 41:815–822
18. Linnet KM, Wisborg K, Obel C, Secher NJ, Thomsen PH, Agerbo E, Henriksen TB (2005) Smoking during pregnancy and the risk for hyperkinetic disorder in offspring. Pediatrics 116:462–467
19. Zhu JL, Olsen J, Liew Z, Li J, Niclasen J, Obel C (2014) Parental smoking during pregnancy and ADHD in children: The Danish National Birth Cohort. Pediatrics 134:e382–e388
20. Thapar A, Rice F, Hay D, Boivin J, Langley K, van Bree M et al (2009) Prenatal smoking might not cause attention-deficit/hyperactivity disorder: evidence from a novel design. Biol Psychiatry 66:722–727
21. Mathews CA, Bimson B, Lowe TL, Herrera L, Budman CL, Erenberg G et al (2006) Association between maternal smoking and increased symptom severity in Tourettés syndrome. Am J Psychiatry 163:1066–1073
22. Pringshem T, Sandor P, Lang A, Prakeshkumar S, Óconnor P (2009) Prenatal and perinatal morbidity in children with Tourette syndrome and attention-deficit hyperactivity disorder. J Dev and Behav Pediatr 30:115–121
23. Santangelo S, Pauls D, Goldstein J, Faraone S, Tsuang M, Leckman J (1994) Tourettés syndrome: what are the influences of gender and comorbid obsessive-compulsive disorder? J Am Acad Child Adolesc Psychiatry 33:795–804
24. Bos-Veneman NGP, Kuin A, Minderaa RB, Hoekstra P (2010) Role of perinatal adversities on tic severity and symptoms of attention deficit/hyperactivity disorder in children and adolescents with a tic disorder. J Dev Behav Pediatr 31:100–106
25. Motlagh M, Katsovich L, Thompson N, Lin H, Kim Y-S, Scahill L, Lombroso PJ et al (2010) Severe psychosocial stress and heavy cigarette smoking during pregnancy: an examination of the pre- and perinatal risk factors associated with ADHD and Tourette syndrome. Eur Child Adolesc Psychiatry 19:755–764
26. Mathews C, Scharf J, Miller L, Macdonald-Wallis C, Lawlor D, Ben-Shlomo Y (2014) Association between pre- and perinatal exposures ad Tourette syndrome or chronic tic disorder in the ALSPAC cohort. The Br J Psychiatry 204:40–45
27. THL 2014: Perinatal statistics—parturients, deliveries and newborns 2013. Statistical Report 23/2014, 13th October (2014) Official Statistics of Finland. http://www.thl.fi/en/web/thlfi-en/statistics/statistics-by-topic/sexual-and-reproductive-health/parturients-deliveries-and-births/perinatal-statistics-parturients-delivers-and-newborns
28. [Update on Current Care guidelines: ADHD (attention-deficit/hyperactivity disorder, children and adolescents)]. Käypä hoito suosituksen päivitystiivistelmä (2012) Duodecim 128:539–540
29. Sund R (2012) Quality of the finnish hospital discharge register: a systematic review. Scand J Public Health 40:505–515
30. Leckman JF, Price RA, Walkup JT, Ort S, Pauls DL, Cohen DJ (1987) Nongenetic factors in Gilles de la Tourette's syndrome. Arch Gen Psychiatry 44:100
31. Burd L, Klug MG, Kerbeshian J (1999) Prenatal and perinatal risk factors for Tourette disorder. J Perinat Med 27:295–302
32. Miller L, Scharf JM, Mathews CA, Ben-Shlomo Y (2014) Tourette syndrome and chronic tic disorder are associated with lower socio-economic status: findings from the Avon longitudinal study of parents and children cohort. Dev Med Child Neurol 56:157–163
33. Ergin I, Hassoy H, Tanik FA, Aslan G (2010) Maternal age, education level and migration: socioeconomic determinants for smoking during pregnancy in a field study from Turkey. BMC Public Health 10:325
34. Thapar A, Cooper M, Eyre O, Langley K (2013) Practitioner Review: What have we learnt about the causes of ADHD? J Child Psychol Psychiatry 54:3–16
35. Halmoy A, Klungsoyr K, Skarven R, Haavik J (2012) Pre- and perinatal risk factors in adults with attention-deficit/hyperactivity disorder. Biol Psychiatry 71:474–481
36. ÓRourke JA, Scharf J, Platko J, Stewart SE, Illmann C, Geller DA et al (2011) The familial association of Tourettés disorder and ADHD: the impact of OCD symptoms. Am J Med Genet B 156:553–560
37. Ekblad M, Gissler M, Korkeila J, Lehtonen L (2013) Trends in smoking during pregnancy in the Nordic Countries. Eur J Public Health. doi:10.1093/eurpub/ckt128
38. England LJ, Kendrick JS, Gargiullo PM, Zahniser SC, Hannon WH (2001) Measures of maternal tobacco exposure and infant birth weight at term. Am J Epidemiol 153:954–960
39. Fantuzzi G, Aggazzotti G, Righi E, Facchinetti F, Bertucci E, Kanitz S et al (2007) Preterm delivery and exposure to active and

passive smoking during pregnancy: a case–control study from Italy. Paediatr Perinat Epidemiol 21:194–200
40. Cerimele JM, Katon WJ (2013) Associations between health risk behaviors and symptoms of schizophrenia and bipolar disorder: a systematic review. Gen Hosp Psychiatry 35:16–22
41. Shah PS (2010) Parity and low birth weight and preterm birth: a systematic review and meta-analyses. Acta Obstet Gynecol Scand 89:862–875
42. Gibson CL, Tibbetts SG (1998) Interaction between maternal cigarette smoking and Apgar scores in predicting offending behavior. Psychol Rep 83:579–586
43. Ferrea S, Winterer G (2009) Neuroprotective and neurotoxic effects of nicotine. Pharmacopsychiatry 42:255–265
44. Wikström R (2007) Effects of nicotine during pregnancy: human and experimental evidence. Curr Neuropharmacol 5:213–222
45. Bublitz MH, Stroud LR (2012) Maternal smoking during pregnancy and offspring brain structure and function: review and agenda for future research. NicotineTob Res 14:388–397
46. Ekblad M, Korkeila J, Parkkola R, Lapinleimu H, Haataja L, Lehtonen L (2010) Maternal Smoking during pregnancy and regional brain volumes in preterm infants. J Pediatr 156:185–190
47. Jauniaux E, Gulbis B, Acharya G, Thiry P, Rodeck C (1999) Maternal tobacco exposure and cotinine levels in fetal fluids in the first half of the pregnancy. Obstet Gynecol 93:25–29
48. Langley K, Heron J, Smith GD, Thapar A (2012) Maternal and paternal smoking during pregnancy and risk of ADHD symptoms in offspring: testing for intrauterine effects. Am J Epidemiol 176:261–268
49. Lichtenstein P, Carlström E, Råstam M, Gillberg C, Anckarsäter H (2010) The Genetics of Autism spectrum disorders and related neuropsychiatric disorders in childhood. Am J Psychiatry 167:1357–1363
50. Plessen KJ, Royal JM, Peterson BS (2007) Neuroimaging of tic disorders with co-existing attention-deficit/hyperactivity disorder. Eur Child Adolesc Psychiatry 1:60–70
51. Cavanna A, Critchley H, Orth M, Stern J, Young M-B, Robertson MM (2011) Dissecting the Gilles de la Tourette spectrum: a factor analytic study on 639 patients. J Neurol Neurosurg Psychiatry 82:1320–1323
52. Rodgers S, Muller M, Kawohl W, Knöpfli D, Rössler W, Castelao E et al (2014) Sex-related and non-sex-related comorbidity subtypes of tic disorders: a latent class approach. Eur J Neurol 21:700–707
53. Grados M, Mathews C (2008) Latent class analysis of Gilles de la Tourette syndrome using comorbidities: clinical and genetic implications. Biol Psychiatry 64:219–225
54. Spencer T, Biederman J, Harding M, ÓDonnell D, Wilens T, Faraone S, Coffey B, Geller D (1998) Distangeling the overlap between Tourettés disorder and ADHD. J Child Psychiat 39:1037–1044
55. Gillberg C, Gillberg IC, Rasmussen P, Kadesjö B, Söderström H, Råstam M et al (2004) Co-existing disorders in ADHD—implications for diagnosis and intervention. Eur Child and Adolesc Psychiatry 13:80–89
56. Nigg J, Nikolas M, Burt SA (2010) Measured gene-by-environment interaction in relation to attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 49:863–873
57. Neuman RJ, Lobos E, Reich W, Henderson CA Sun LW, Todd RD (2007) Prenatal smoking exposure and dopaminergic genotypes interact to cause a severe ADHD subtype. Biol Psychiatry 61:1320–1328
58. Brookes K-J, Mill J, Gindalini C, Curran S, Xu X, Knight J et al (2006) A common haplotype of the dopamine transpoter gene associated with attention-deficit/hyperactivity disorder and interacting with maternal use of alcohol during pregnancy. Arch Gen Psychiatry 63:74–81
59. Ford RP, Tappin DM, Schluter PJ, Wild CJ (1997) Smoking during pregnancy: how reliable are maternal self-reports in New Zealand? J Epidemiol Community Health 51:225–246